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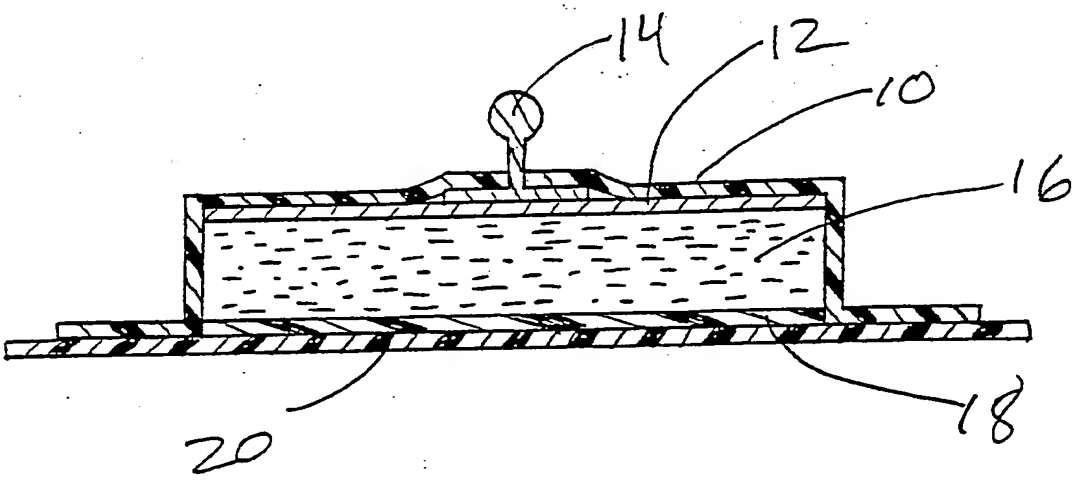
(54) Title: IONTOPHORESIS ELECTRODE



(57) Abstract

An improved iontophoresis electrode employing a current distributing member (12) and a drug reservoir (16) containing an ionic drug. The drug reservoir (16) is applied to the skin of a patient, and includes a charge selective ion permeable membrane (18) adapted to contact the skin, through which the ionic drug is delivered.

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IONTOPHORESIS ELECTRODE

CROSS REFERENCE TO RELATED APPLICATIONS

Reference is made to concurrently filed, commonly assigned U.S. patent application entitled "IONTOPHORESIS", Serial No. _____, by Phipps, filed as of the date of this application. This application is hereby incorporated by reference in its entirety. Reference is also made to previously filed, commonly assigned U.S. patent application entitled "IONTOPHORETIC DRUG DELIVERY", Serial No. 154,566, filed February 10, 1988 by Untereker et al.

BACKGROUND OF THE INVENTION

This invention relates to methods and apparatus for transdermal medicament delivery and to improvements therein. More specifically, this invention relates to improved methods and apparatus for active (as opposed to passive) transdermal, ambulatory drug delivery. Yet more particularly, this invention relates to increasing the efficiency of iontophoresis devices and to improved methods of making and using such devices.

Recently, there has been a renewed interest in the technology of iontophoresis. Iontophoresis has been found to be useful in the transdermal administration or introduction of lidocaine hydrochloride, hydrocortisone, acetic acid, flouride, penicillin, dexamethasone sodium phosphate, and many other drugs. Perhaps the widest use of iontophoresis is the diagnosis of cystic fibrosis using pilocarpine nitrate iontophoresis.

In presently known iontophoresis devices, at least two electrodes are used. Both these electrodes are disposed so as to be in intimate electrical contact with some portion of the skin. The "active" electrode is the electrode from which the ionic drug is delivered into the body. The "indifferent" or ground electrode serves to close the electrical circuit through the body. A battery or other current source is coupled to the electrode to

provide the electrical force to drive the drug into the body. For example, if the ionic substance to be driven into the body is positively charged, then the positive electrode (the anode) will be the active electrode and the negative electrode (the cathode) will serve to complete the circuit. If the ionic substance to be delivered is negatively charged, then the negative electrode will be the active electrode and the positive electrode will be the indifferent electrode. Of course, simultaneous delivery of drugs from both of the electrodes is also possible.

Generally, iontophoresis electrodes include a reservoir of the drug, typically compounded as a salt of the drug, for example a flouride or sulfate. These reservoirs may take the form of preformed gel bodies, such as disclosed in U.S. Patent No. 4,382,529 issued to Webster, solid adhesive bodies as disclosed in U.S. Patent No. 4,416,274, issued to Jacobson, or fluid reservoirs as disclosed in U.S. Patent No. 4,250,878, issued to Jacobsen. Electrical current is typically applied to the fluid reservoir by means of a current distributing member, which may take the form of a metal plate, a foil layer, a conductive screen, or a dispersion of conductive particles within the drug reservoir.

Typically, the current distributing member in iontophoresis electrodes has been constructed of an inert material, such as stainless steel or platinum. However, more recently use of sacrificial current distributing members which are oxidized or reduced themselves during delivery of the drug has been discussed. Use of sacrificial current distributing members can avoid the pH changes and other adverse effects associated with the hydrolysis of water which generally accompanies the use of inert current distributing members. Electrodes with sacrificial current distributing members are disclosed in U.S. Patent No. 4,744,787, issued to Phipps et al, incorporated herein by reference in its entirety. Such

electrodes are also discussed in the above-cited copending application by Untereker et al, also incorporated herein by reference in its entirety.

An alternative approach to avoiding the adverse effects associated with hydrolysis of water at the current distributing member is disclosed in the published PCT Patent Application No. WO 87/04936, published August 27, 1987, by Sanderson et al, corresponding to U.S. Patent No. 4,722,726. This electrode system is also described in the article "Noninvasive Delivery of a Novel Inotropic Catecholamine: Iontophoretic Versus Intravenous Infusion in Dogs" by Sanderson et al, published in the Journal of Pharmaceutical Sciences, Vol. 76, No. 3, March 1987, pp. 215-218. In this electrode system, an inert current distributing member is used and the electrode is divided into an upper chamber filled with a buffer and a lower chamber containing the ionic drug. The upper chamber is separated from the lower chamber by means of an ion selective membrane. As described, it is apparently intended that the buffer solution in the upper chamber mitigate the effects of hydrolysis of water, and that the ion selective membrane isolate the drug from the contents of the upper chamber.

In electrodes including fluid reservoirs, as disclosed in U.S. Patent No. 4,250,878 issued Jacobson, delivery of the drug typically takes place through a microporous membrane. Typically, such membranes are permeable based on size, and therefore must be permeable to any ion equal to or smaller than the drug ion intended to be delivered. In U.S. Patent No. 4,640,689, issued on February 3, 1987 to Sibalis, an iontophoresis electrode including a gel type drug reservoir provided with a semipermeable membrane is disclosed. This reference also suggests the use of an "ion selective retention gel" intermediate the drug reservoir and the semipermeable membrane. The ion to be retained by the gel is not discussed.

SUMMARY OF THE INVENTION

Typical iontophoresis electrodes must be permeable to the drug which they deliver. Generally, this has resulted in the electrode also being permeable to molecular species of equal or smaller size. During delivery of the drug, therefore, it is to be expected that ions of charge opposite to that of the drug to be delivered will migrate into the electrode. For example, in an electrode which delivers propranolol, compounded in the reservoir in the form of propranolol hydrochloride, a positive drug ion will be delivered. Because the electrode will be applied to the skin, it is to be expected that sodium chloride will be available at the electrode/skin interface, either from the tissues of the body or contained in sweat. Thus, as the positively charged propranolol ion migrates out of the electrode under the influence of the electrical field, chlorine ions present at the skin migrate into the electrode and provide an alternate ionic conductor. Because of the relatively smaller size of the chlorine ion, it migrates more readily under the influence of the electrical field than the typically larger drug ions. It is believed that this process dramatically reduces the efficiency of most iontophoresis electrodes.

The present invention provides a charge selective ion premeable membrane which is preferentially permeable to ions having the same charge as the drug ion. This membrane reduces transport of oppositely charged ions across the electrode/skin interface. The effect of sodium, chloride or other ions present in the skin which would otherwise provide an alternative ionic current path is thus minimized. By reducing the availability of other mobile charge carriers in the drug reservoir, efficiency of delivery of the ionic drug is increased.

This electrode structure is particularly beneficial in the context of an electrode employing a sacrificial current distributing member, as discussed above. By providing a current distributing member which is oxidized

or reduced at a voltage less than that of water (e.g. silver or silver/silver chloride) in conjunction with a current limited power source, electrolysis of water is reduced or eliminated. This is discussed in more detail in U.S. Patent Application Serial No. 154,566, for "IONTOPHORETIC DRUG DELIVERY", filed February 10, 1988 by Untereker et al, incorporated herein by reference in its entirety. Such sacrificial current distributing members are also disclosed in U.S. Patent No. 4,744,787 issued to Phipps et al, and also incorporated herein by reference in its entirety.

Eliminating hydrolysis in the electrode prevents formation of charged species (OH^- and H_3O^+) within the electrodes. This further reduces the availability of ionic current carriers other than the drug ions. Thus, the combination of the sacrificial current distributing member with the charge selective ion permeable membrane provides a particularly advantageous iontophoresis electrode.

BRIEF DESCRIPTION OF THE DRAWING

Fig. 1 shows a cross sectional view of an iontophoresis electrode embodying the present invention.

DETAILED DESCRIPTION OF THE INVENTION

Fig. 1 shows a sectional view through an iontophoresis electrode according to the present invention. The electrode is mounted within a non-conductive housing 10, which contains a current distributing member 12, here illustrated as a metallic foil or plate. Current distributing member 12 may also take the form of a screen or a dispersion of conductive particles within the drug reservoir 16. Reservoir 16 contains the drug to be delivered. Current distributing member 12 is preferably a sacrificial current distributing member. Alternatively, member 12 may be fabricated of an inert metal such as platinum or stainless steel.

In one embodiment of the invention, current distributing member 12 takes the form of a sacrificial current distributing member, which is readily oxidized or reduced. If the drug ion to be delivered is positively charged, the electrode (anode) would include a current distributing member 12 made of a readily oxidizable metal, such as silver, and the drug would be compounded with a counterion which forms a neutrally charged and preferably insoluble compound when reacted with ionic silver. One example would be lithium chloride. As the silver in the current distributing member is oxidized, it will react with the chlorine ions within the reservoir 16 to form a silver chloride precipitate. The positive lithium ions will be free to migrate through the reservoir 16.

If the drug ion to be delivered is negatively charged, the electrode (cathode) would include a current distributing member 12 made of readily reducible material, such as silver/silver chloride, and the drug would be compounded with a counterion which forms a neutrally charged and preferably insoluble compound when reacted with chloride ion, for example, silver or copper salicylate. As ionic silver in the silver chloride portion of member 12 is reduced, the released chlorine ions will react with the silver or copper counterions compounded with the drug to form insoluble silver chloride. The negative salicylate ions will be free to migrate through the reservoir 16.

Current distributing member 12 is coupled to a snap connector 14, which facilitates connection of the electrode to a source of electrical current. Typically, such power sources used with the electrode will be current limited, so that the electrical potential at the electrode will be established by the chemistry of the electrode itself.

Drug reservoir 16 contains the ionic drug to be delivered. Examples of cationic drugs deliverable by iontophoresis include lithium and pilocarpine. Examples

of anionic drugs appropriate for delivery by iontophoresis include salicylate and flouride. Preferably, this reservoir takes the form of a gel, but may take the form of a liquid. Preferably, drug reservoir 16 is free of ionic or readily ionizable material other than the drug to be delivered. For example, the matrix may take the form of a polar, nonionic gel, such as a polyvinyl alcohol gel or a gel as disclosed in EPO Patent No. 0 060 451, issued on September 17, 1986 to Lattin et al. This EPO patent is incorporated by reference herein in its entirety.

A charge selective ion permeable membrane 18 is applied to the lower surface of reservoir 16. Membrane 18 forms the interface between the reservoir 16 and the skin of the patient to whom the electrode is applied. For example, if the electrode is used to deliver a negatively charged drug, membrane 18 would then be an anion permeable membrane. Examples of anionic and cationic selective membranes are described in the article "ACRYLIC ION-TRANSFER POLYMERS", by Ballestrasse et al, published in the Journal of the Electrochemical Society, November 1987, Vol. 134, No. 11, pp. 2745-2749. An additional appropriate anion exchange membrane would be a copolymer of styrene and divinyl benzene reacted with trimethylamine chloride to provide an anion exchange membrane. (See "Principles of Polymer Systems", by F. Rodriguez, McGraw-Hill Book Co., 1979, pgs. 382-390.) These articles are incorporated herein by reference in their entirety. An additional appropriate cationic permeable material for use in conjunction with delivery of a positively charged drug would be a sulfonated styrene polymer or a sulfonated fluorocarbon polymer, e.g. Nafion™ membranes, a product of Dupont. Before applying the membrane 18 to the reservoir 16, it should be saturated with the ionic drug to be delivered. Applied to the exterior of housing 10 and membrane 18 is a release liner 20, which serves to prevent the reservoir 16 and membrane 18 from drying out during storage.

In the preferred embodiment, the provision of a sacrificial current distributing member in conjunction with an appropriately compounded drug (e.g. silver current distributing member and lithium chloride prevents the generation of ions within the electrode which have the same charge as the drug. The provision of a charged selective membrane 18 on the exterior of reservoir 16 substantially prevents migration of charged particles having a charge opposite to that of the drug into the reservoir. As such, in its preferred embodiment, the charged drug ion to be delivered will be substantially the only ionic material within the reservoir, and should be free to migrate through the reservoir 16 without any substantial competition. This provides a significant increase in efficiency of drug delivery. The membrane is also believed valuable in conjunction with iontophoresis electrodes employing insert current distributing members, in that it will at least reduce the availability of competing, mobile ions within the reservoir 16.

As noted above, the invention may be practiced in conjunction with inert current distributing members. This approach is particularly valuable in conjunction with the delivery of drugs which take the form of weak acids or weak bases. In these electrodes, hydrolysis of water is deliberately induced, with the hydrolysis product combining with the drug as compounded to produce an ionic, mobile species. For example, a weakly acidic drug D may be placed in a drug reservoir including a platinum current distributing member, which functions as the anode of the iontophoresis system. Hydrolysis of water occurs at the anode, with excess hydrogen ions combining with the drug to produce a charged species DH^+, which is substantially the only charged species within the reservoir. Corresponding systems employing weakly basic drugs may also be produced. Such systems are described in more detail in the above cited patent application Serial No.

154,566, by Untereker et al, previously incorporated by reference.

The invention of the present application is also applicable to electrodes as described in the concurrently filed application by Phipps, cited above, which employs a charge selective ion permeable membrane attached to the current distributing member. In such case, the charge selective ion permeable material applied to the current distributing member is permeable to ions having a polarity opposite to that of the drug. This membrane prevents contact between the drug ions in the reservoir and the current distributing member and prevents passage of ions formed during the oxidation or reduction of a sacrifical current distributing member into the drug reservoir.

Although disclosed in the form of a completed, disposable electrode, the present invention is also believed valuable in the context of an electrode which has a removable or reusable drug reservoir, as disclosed in the above cited EPO patent by Lattin et al. In this case, it is anticipated that the drug reservoir would be separately packaged, and include the ion selective membrane. The reservoir and membrane would be attached at a later time to the current distributing member, which might be permanently mounted to an iontophoresis device.

In conjunction with the above description, we claim:

II. CLAIMS

1. An iontophoresis electrode, comprising:
a conductive, current distributing member;
means for coupling said current distributing member to a source of electrical current;
a reservoir containing an ionic or ionizable drug to be delivered; and
a charge selective material applied to the exterior of said reservoir, selective for ions having the same charge as said drug.

2. An iontophoresis electrode, comprising:
a current distributing member fabricated of a material which is readily oxidized or reduced at a voltage less than the voltage required to hydrolyze water;
connector means for connecting said current distributing member to a source of electrical current;
reservoir means coupled to said current distributing member, said reservoir means containing an ionic drug compounded with a counter ion which reacts with said material of which said current distributing member is fabricated, after said material is oxidized or reduced, to produce a neutrally charged compound within said reservoir; and
a charge selective material applied to the exterior of said reservoir, selective for ions of the same charge as said drug.

3. A method of transdermally delivering an ionic drug, comprising:
selecting an iontophoresis electrode containing an ionic or ionizable drug, said electrode including a reservoir which contains said ionic drug and a charge

selective membrane fabricated of a material permeable to ions having the same charge as said drug;

applying said electrode to the skin of a patient, such that said membrane is located between said reservoir and said skin of said patient; and

coupling said electrode to a source of direct electrical current.

4. A method of iontophoretically introducing an ionic drug, comprising the steps of:

selecting an iontophoretic electrode of the type including a current distributing member fabricated of a material which is readily oxidized at a voltage lower than that required to hydrolyze water, and including a reservoir containing an ionic drug compounded with a counter ion which reacts with said material of which said current distributing member is fabricated, after said material is oxidized or reduced, to produce a neutrally charged compound within said reservoir and including a charge selective membrane applied to said drug reservoir, said charge selective membrane selective for ions having the same charge as said ionic drug;

applying said electrode to the skin of a patient such that said charge selective membrane is located between the skin of said patient and said drug reservoir; and

coupling said electrode to a source of direct electrical current.

5. A method of fabricating an iontophoresis electrode, comprising the steps of:

selecting an ionic or ionizable drug to be delivered;

including said drug within a reservoir through which said drug is permeable; and

applying a charge selective material to the exterior of said reservoir, said charge selective material permeable to ions having the same charge as said drug.

6. A method of fabricating an iontophoresis electrode, comprising the steps of:

selecting an ionic drug to be delivered;

selecting a sacrificial current distributing member fabricated of a material readily oxidizable or reduced by application of a voltage less than required to hydrolyze water;

compounding said ionic drug with a counter ion which will react with the material of which said current distributing member is fabricated, after said material is oxidized or reduced, to produce a neutrally charged compound and placing said compounded ionic drug into a reservoir through which said ionic drug is permeable; and

applying a charge selective material to the exterior of said reservoir, said charge selective material permeable to ions having the same charge as said ionic drug.

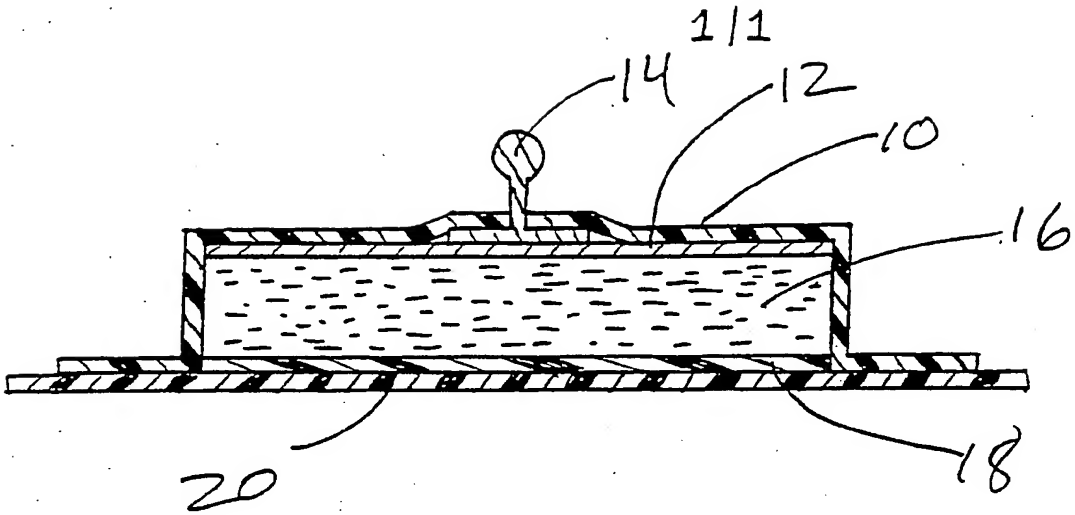

Fig.1

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US89/04841

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC (4): A61N 1/00
U.S. Cl. 604/20

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
U.S.	604/20, 890.1; 128/783, 798, 802; 424/447, 448, 449

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No [13]
A	US, A, 4,416,274 (JACOBSEN ET AL) 22 November 1983, see abstract.	1-6
A	JP, A, 60-203,270 (TAKAYOSHIT) 14 October 1985, see abstract.	1-6
X Y	US, A, 4,640,689 (SIBALIS) 03 February 1987 See column 2, line 20 through column 8, line 36.	1, 3, 5 2, 4, 6
A	US, A, 4,720,334 (DUBOIS ET AL) 19 January 1988, see abstract.	1-6
X	US, A, 4,722,726 (SANDERSON ET AL) 02 February 1988, see column 5, line 15 through column 9, line 11.	1
X	US, A, 4,731,049 (PARSI) 15 March 1988 See column 2, line 20 through column 4, line 35.	1
Y	US, A, 4,744,787 (PHIPPS ET AL) 17 May 1988 See column 3, line 35 through column 9, line 50.	2, 4, 6

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
05 December 1989	18 JAN 1990
International Searching Authority	Signature of Authorized Officer
ISA/US	Ralph Lewis

Form PCT/ISA/210 (second sheet) (Rev. 11-87)

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

A	US, A, 4,747,819 (PHIPPS ET AL) 31 May 1988 See abstract.	1-6
Y	US, A, 4,752,285 (PETELENZ ET AL) 21 June 1988, see column 7, line 63 through column 16, line 60.	2, 4, 6
A	Journal of Pharmaceutical Sciences, Vol. 76, No. 3, March 1987, (SANDERSON ET AL), "Noninvasive Delivery of a Novel Inotropic Catecholamine: Iontophoretic Versus Intravenous in Dogs", pages 215-218.	1-6

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☐ Claim numbers . because they relate to subject matter [12] not required to be searched by this Authority, namely:

2. ☐ Claim numbers . because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out [13], specifically:

3. ☐ Claim numbers_____, because they are dependent claims not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.